UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

Ex parte DARIO CREMASCHI and CRISTINA PORTA

Appeal No. 2006-2451
Application No. 09/988,150

HEARD: October 17, 2006

Before ADAMS, GREEN, and LEBOVITZ, Administrative Patent Judges.

LEBOVITZ, Administrative Patent Judge.

DECISION ON APPEAL

This appeal involves claims to a method for intranasal administration of a protein composition. The examiner has rejected the claims as obvious. We have jurisdiction under 35 U.S.C. § 134. We affirm.

Background

The nasal mucosa is an alternative route which has recently been exploited for the administration of proteins. Bomberger,[1] column 1, lines 21-25. Several different approaches to accomplish nasal delivery have been used. Microspheres encapsulating proteins have been used to deliver protein drugs to the nasal passageways. Id., column

[1] Bomberger et al. (Bomberger), U.S. Patent 5,879,712, issued Mar. 9, 1999 (cited by the Examiner in the rejection under § 103).

4, lines 47-51. Surfactants, which increase the permeability of nasal mucous membranes, have been formulated with proteins to enhance their delivery across the nasal membranes. Specification, page 1, lines 24-28. Nasal transit retardants have also been used to facilitate protein absorption by the nasal mucosa membranes. Id., page 2, lines 10-13. All of these approaches have disadvantages. Id., page 2, lines 6-22. The instant application describes microparticles having adsorbed protein and a specific antibody to the protein for intranasal administration. Id., page 1, lines 5-7.

Discussion

Claim construction

Claims 11-13 and 15-19 are on appeal. Claims 20, 22, and 24-28 have been found allowable. Answer, page 2. (Claims 12 and 21 are also objected to by the Examiner. Id. This objection has not been presented for our review.) The claims stand or fall together since Appellants have not provided separate reasons for the patentability of any individual claim, but have argued the claims as a group. See 37 C.F.R. § 41.37. We have selected claim 11 as representative for the purposes of deciding this appeal. It reads as follows:

> 11. A method for intranasally administering a composition comprising a microparticle having a protein and an antibody adsorbed thereon, wherein said administering comprises contacting a microparticle having a protein and an antibody thereon with the nasal mucosa of a patient in need thereof, wherein said antibody is an immunoglobulin specific for the protein.

Obviousness

Claims 11-13 and 15-19 stand rejected under 35 U.S.C. § 103(a) as unpatentable over Smith[2] in view of Bomberger and Almeida.[3]

Smith provides a composition for oral administration of proteins. Smith, page 1, lines 3-6. The composition comprises a protein, an antibody which specifically binds to the protein, and polymer beads. Id., page 4, lines 11-16. The composition is targeted to M cells, a type of cell which occurs "in the epithelial lining of the Peyer's patch lymphoid follicles of the intestine." Id., page 2, lines 19-20. "M cells are able to endocytose small amounts of particulate matter from the gut lumen for presentation to the gut associated lymphoid tissue (GALT)." Id., page 2, lines 27-30. "The theory behind the use of such a composition is that an antibody raised against a biologically active peptide or protein will not only bind specifically to that peptide or protein but will also bind non-specifically to the M cell surface so allowing a bead or particle carrying the peptide or protein and the antibody to be carried into and across M cells." Id., page 4, lines 18-24. Examples of proteins that can be orally administered include hormones, interferons, blood factors, and antigenic proteins for eliciting an immune response. Id., page 6, line 5-31. "The biologically active material [protein] will generally be adsorbed onto the surface of the beads and the antibody is added so as to form a complex between the material and the antibody and to leave part of the antibody free for non-specific binding to the M cells." Id., page 7, lines 5-9.

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[2] Smith et al. (Smith), WO 94/28879, published Dec. 22, 1994
[3] Almeida et al. (Almeida), Journal of Drug Targeting, 3:455-467, 1996

Almeida is a review of nasal vaccine administration, describing the structure of the nasal passageway, mechanisms of how proteins are absorbed intransally, and studies involving the delivery of proteins to the nasal mucosa. Bomberger describes microparticles which can be loaded with drugs for nasal delivery. Bomberger, column 1, lines 5-12; column 4, lines 48-51. The patent specifically describes alginate microparticles loaded with a protein, such as intercellular adhesion molecule ICAM-1. Id., column 3, lines 62-65.

According to the Examiner, Smith teaches the same composition comprising protein and microparticles which is recited in claim 11, but does not describe it for intranasal administration. Answer, page 4. Bomberger and Almeida are cited by the Examiner for teaching intranasal administration of proteins. Id., page 5. The Examiner concludes:

> [I]t would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to include nasal administration of the composition taught by Smith et al. because nasal administration of microparticles containing peptides and proteins was well established in the art as taught by Bomberger et al. (US Patent No. 5,879,712). Further, one would have been motivated to do so because Almeida et al. teach that nasal delivered vaccines are advantageous compared to other mucosal surfaces because of the valuable surface area of the nasal mucosa, the easier accessibility and administration that increases patient compliance and venous flow that bypasses the portal system, thus preventing first-pass metabolism in the liver (page 457, 1st column).

Id., pages 5-6.

Appellants challenge the rejection, arguing that there would have been no motivation with an expectation of success "to perform the claimed method." Brief,

page 4. They state that Bomberger describes controlled delivery of drugs to the nasal passageway using microparticles in which "the drug to be delivered is contained within the microparticle," not adsorbed onto the microparticle as recited in claim 11. Id., page 5. They argue that this would "lead one away from the claimed invention." Id. Appellants also contend that "a prima facie case is rebutted by the data of record in the application which demonstrates greater than 400,000 times more particles absorbed through the nasal mucosa compared to the intestines." Id., page 6.

A proper analysis under § 103 requires consideration of whether the prior art would have suggested to those of ordinary skill in the art that they should make the claimed subject matter, and whether the prior art would also have revealed that, in making the claimed subject matter, those of ordinary skill would have a reasonable expectation of success. In re Vaeck, 947 F.2d 488, 493, 5 USPQ 1529, 1531 (Fed. Circ. 1988).

We agree with the Examiner that the person of ordinary skill in the art would have been motivated to have utilized Smith's composition for intranasal administration. Smith describes experiments which show that microparticles coated with protein and an antibody specific for that protein enter intestinal (gut) M cells after oral ingestion "more readily" than microparticles coated only with the protein. Smith, pages 13-15. The enhanced uptake was shown to be 2x, 5x, and 10x greater, depending on the particular protein measured. Id., page 13, lines 21 and 26; page 14, line 3. Almeida expressly teaches that both oral and nasal uptake are mediated by the M cells in the mucosal epithelium. Almeida, page 457, column 2-page 458, column 2. It also teaches that the nasal mucosa tissue (NALT) and gut-associated lymphoid tissue (GALT) system are

part of the common mucosal immune system. Id, page 455, column 2-page 456, column 1. Many of the approaches utilized for oral administration are described by Almeida as having been used successfully for nasal administration. For example, cholera toxin was used as an adjuvant in oral and nasal delivery experiments. Id., page 459, column 2. Microspheres were also used with success in both the oral and nasal environment to deliver proteins, including tetanus toxoid adsorbed to PLA microspheres. Id., page 463, column 1. The use of Smith's composition for nasal delivery would have been considered by a person of ordinary skill in the art a repetition of the paradigm described by Almeida in which compositions for oral administration are used for the intranasal route for its disclosed advantages, including higher permeability (id., page 457) and increased patient compliance (id., page 463).

Appellants argue that Bomberger teaches away from the claimed subject matter because "encapsulated microparticles are different and not generally applicable to any situation as in the Smith delivery vehicles." Reply Brief, page 4. See also Brief, page 5. We do not agree. The Examiner relies on Bomberger for its general teaching that microparticles can be utilized for intranasal administration, not for the microparticle composition which is administered. Answer, pages 5 and 7. Smith is cited by the Examiner for the particular microparticle composition which is claimed; Appellants do not distinguish their claimed "microparticle having a protein and antibody adsorbed thereon" from Smith's composition.

We also agree with the Examiner that there would have been a reasonable expectation of success. Answer, page 6. According to Almeida, "evidence that the nasal administration of antigens can be a useful route of immunisation has been

provided since the 1920's." Id., page 458, second column. "Nasal vaccination has been investigated by administering antigens together with adjuvants." Id., page 459, column 1. In particular, microspheres have been utilized to deliver antigens through the nasal route, either by encapsulating or adsorbing the antigen on the microsphere surface. Id., page 462, column 2-463, column 1. Almeida states that "[n]asal immunisation studies carried out by several independent laboratories suggest that the use of a respiratory mucosal delivery route can be protective from some infections." Id. Finally, as discussed above, similarities in the mechanism (e.g., M cells uptake) between oral and nasal administration would have reasonably suggested that a composition which works orally would also work nasally. "[A] general, albeit, imperfect correlation between a drug's lipophilicity and its colonic absorptivity" was found to be sufficient to establish a reasonable expectation of success. Alza Corp. v. Mylan Labs, 464 F.3d 1286, 1298, 80 USPQ2d 1286, 1298 (Fed. Cir. 2006). Thus, we conclude that the Examiner has provided adequate evidence to establish a prima facie case of obviousness.

Appellants argue that "that the intestinal absorption and nasal absorption are similar - as opposed to the 'superior advantages' espoused by the Examiner in providing some reason to combine Smith with Almeida." Reply Brief, page 3. We are not persuaded by this argument. Almeida expressly states that intranasal immunization appears to be superior to the oral route "to achieve a comprehensive immune response." Almeida, page 463, line spanning columns 1-2. It also states that nasal mucosa has "higher permeability" when compared to other mucosal surfaces." Id., page 457, column 1. Furthermore, the Examiner also cited advantages of the nasal route

which are independent of the physiological similarities, including ease of administration and increased patient compliance. Answer, page 5. In sum, we find the strong teachings about the value of intranasal delivery described in Almeida hard to reconcile with Appellants' position.

"When the PTO shows prima facie obviousness, the burden then shifts to the applicant to rebut it. In re Dillon, 919 F.2d 688, 692 [16 USPQ2d 1897] (Fed. Cir. 1990) (en banc). Rebuttal may take the form of 'a comparison of test data showing that the claimed compositions possess unexpectedly improved properties . . . that the prior art does not have, that the prior art is so deficient that there is no motivation to make what might otherwise appear to be obvious changes, or any other argument . . . that is pertinent.' Id. at 692-93 (citations omitted)." In re Harris, 409 F.3d 1339, 1343, 74 USPQ2d 1951, 1954 (Fed. Cir. 2005). Appellants argue that prima facie obviousness is rebutted by their showing that 400,000 times more particles are absorbed through the nasal mucosa than through the intestine. Brief, page 6.

The Examiner dismisses these results for two primary reasons. First, he states that results obtained by the in vivo intestinal model used by Smith cannot be compared to the results generated by Appellants using an in vitro nasal model. Answer, page 9. Secondly, the Examiner argues that Appellants' higher results in the nasal mucosa would have been expected from Almeida's teaching that "the nasal administration of drugs exploits the high permeability of the nasal mucosa when compared to other mucosal surfaces." Id., page 11.

We agree with the Examiner that the results are not sufficient to rebut the prima facie obviousness of the claimed subject matter, but we rely on different reasoning.

Appellants compare their rabbit nasal mucosa data (specification, page 6, Example 1) to Smith's rat intestinal data (specification, page 3, lines 11-14). Appellants have not addressed whether the calculated improvement in delivery could be attributed to species differences (rabbit versus rat) in transport rates, rather than being a property of the tissues, alone.

In addition, Smith utilized bovine growth hormone (bGH) in their oral delivery studies, which is a 191 amino acid protein. Specification, page 3, lines 8-14; page 1, line 28. Appellants, in contrast, used insulin, which contains a total of 51 amino acids. Id., page 13, Table 2; page 1, line 16. The protein type (growth hormone versus insulin) and size (191 amino acids versus 51 amino acids) could account for the transport differences. During oral argument, Appellants argued that the specification states that once a threshold is reached of about 51 amino acids, the size of the protein should not matter. Id., page 1, lines 12-17. We do not find this argument persuasive because Appellants own data summarized in Table 1 on page 12 of the application shows that the net transport rate across the nasal mucosa varied, depending on the protein utilized. For example, insulin + antibody had a net rate of about 68.32, while BSA + antibody had a net rate of about 9. Appellants also acknowledge in the specification that "there are appreciable differences for the same peptide from species to species, even from individual to individual of the same species." Id., page 1, lines 17-20.

In sum, we do not find the evidence of "unexpected results" as presented in this appeal to be adequate to rebut the case of prima facie obviousness. The rejection of claim 11 is affirmed. Claims 12, 13, and 15-19 fall with claim 11 since separate reasons for their patentability were not presented. Since our explanation as to why the results

are insufficient was not previously identified by the Examiner, we designate this a new ground of rejection to afford Appellants the opportunity to respond. In re Kumar, 418 F.3d 1361, 1367, 76 USPQ2d 1048, 1051 (Fed. Cir. 2005).

No time period for taking any subsequent action in connection with this appeal may be extended under 37 CFR § 1.136(a).

This decision contains a new ground of rejection pursuant to 37 CFR § 41.50(b) (effective September 13, 2004, 69 Fed. Reg. 49960 (August 12, 2004), 1286 Off. Gaz. Pat. Office 21 (September 7, 2004)). 37 CFR § 41.50(b) provides "[a] new ground of rejection pursuant to this paragraph shall not be considered final for judicial review." 37 CFR § 41.50(b) also provides that the appellant, WITHIN TWO MONTHS FROM THE DATE OF THE DECISION, must exercise one of the following two options with respect to the new ground of rejection to avoid termination of the appeal as to the rejected claims:

> (1) *Reopen prosecution.* Submit an appropriate amendment of the claims so rejected or new evidence relating to the claims so rejected, or both, and have the matter reconsidered by the examiner, in which event the proceeding will be remanded to the examiner. . . .
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> (2) *Request rehearing.* Request that the proceeding be reheard under § 41.52 by the Board upon the same record. . . .

AFFIRMED, 37 CFR 41.50(b)

DONALD E. ADAMS)
Administrative Patent Judge)
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LORA M. GREEN)
Administrative Patent Judge) APPEALS AND
)
) INTERFERENCES
)
RICHARD M. LEBOVITZ)
Administrative Patent Judge)

RML/jlb

C. IRVIN MCCLELLAND
OBLON, SPIVAK, MCCLELLAND,
MAIER & NEUSTADT, P.C.
1940 DUKE STREET
ALEXANDRIA, VA 22314